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Adherence to Study Drug in a Stroke Prevention Trial

Akshatha Kiran, BS¹, Catherine M. Viscoli, Ph.D.¹, Karen L. Furie, M.D., MPH², Mark Gorman, M.D.³, Walter N. Kernan, M.D.¹, IRIS Trial Investigators

¹Yale School of Medicine, New Haven, CT;

²Alpert Medical School of Brown University, Providence, RI;

³Maine Medical Center, Portland, ME.

Abstract

OBJECTIVE.—Standards for reporting and analyzing adherence to medical therapy have recently improved due to international consensus efforts. If applied to clinical trial research in patients with stroke, these improvements have the potential to identify when in the sequence of trial operations participants are at risk for non-adherence and opportunities to safeguard adherence.

METHODS.—We analyzed three phases of adherence according to the European Society for Patient Adherence, COMpliance, and Persistence (ESCOMP) Medication Adherence Reporting Guideline (EMERGE) taxonomy in the Insulin Resistance Intervention after Stroke (IRIS) trial: initiation (did patient start drug), implementation (did patient take a drug holiday, defined as temporary cessation lasting 14 days), and persistence (did patient prematurely and permanently discontinue drug). IRIS was a randomized, placebo controlled, double-blind trial testing pioglitazone to prevent stroke or myocardial infarction in patients with a recent ischemic stroke or transient ischemic attack. Adherence was classified by self-report. Researchers used coaching algorithms to seek adherence recovery if participants went off drug.

RESULTS.—During 2005–2013, 3876 participants were enrolled from 179 sites in seven countries and followed for a mean of 4.8 years. Less than 1% of participants in each group did not initiate study drug. 20% of patients assigned to pioglitazone and 17% assigned to placebo took at least one drug holiday. 36% and 30%, respectively, discontinued the study drug prematurely with or without a prior holiday. The risk for stopping the study drug (temporarily or permanently) in the first year after randomization was twice the risk in each of the subsequent four years. This was true both for patients assigned to active therapy and placebo. More participants assigned to pioglitazone, compared to placebo, took a drug holiday or permanently stopped study drug, but the

Corresponding Author: Walter N. Kernan, M.D., Room 407A, ES Harkness Hall A, 367 Cedar Street, New Haven, CT 06510; Telephone: 203-785-7208; Fax: 203-737-3306; walter.kernan@yale.edu. **Contact Information for Other Authors:** Ms. Kiran: 919-744-0456, akshatha.kiran@yale.edu; Dr. Viscoli: 203-674-755, catherine.viscoli@yale.edu; Dr. Furie: 401-444-8715, kfurie@lifespan.org; Dr. Gorman: 224-515-6518, gorman1959@mac.com.

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difference in rates of discontinuation was only evident in year one. In years two through five, rates of discontinuation were similar in the two treatment groups. The difference in rates during year one was the result of adverse effects related to the active study drug, pioglitazone. During the remainder of the trial, the attribution of discontinuations to adverse effects potentially related to pioglitazone was reduced but still higher in those assigned to active drug. Other reasons for discontinuation were similar between treatment groups and were largely unrelated to pharmacodynamic effects of the study drug. Rates of discontinuation varied widely among research sites.

CONCLUSION.—Patients in a drug trial for stroke prevention are at greatest risk for premature drug discontinuation early after randomization. Reasons for discontinuation change over time. Variable discontinuation rates among sites suggests that adherence can be improved by using best practices from high-performing sites.

Keywords

Ischemic Stroke; Transient Ischemic Attack; Pioglitazone; Insulin Resistance; Prevention

INTRODUCTION

Participants in a clinical trial can influence its success by their adherence to the study intervention. In the case of an effective experimental therapy, good adherence will widen the observed outcome rate difference between compared groups of participants and preserve the statistical power of the study to disprove the null hypothesis. For an ineffective therapy, good adherence guards against criticism that a meaningful effect was missed due to poor execution. For any experimental therapy, effective or not, good adherence is needed to accurately estimate the frequency of adverse events in the compared interventions and, thereby, facilitate safe application in clinical practice. There is also a direct benefit of adherence to research participants; when participants take their assigned treatment as prescribed, they assure that the effort of each individual participant is fruitful and contributes to the purpose for which they have sacrificed and often put themselves at risk.

Despite these benefits, clinical trials of long-term therapy in all fields typically struggle to maintain adherence¹. In a meta-analysis of medication adherence among participants in 7 clinical trials of oral therapy for type 2 diabetes, 32% of participants prematurely discontinued use of study drug (95% confidence interval 17–47)². In compiled data from 21 phase IV trials of hypertension therapy about half of participants stopped taking their assigned therapy within a year.³

Clinical trials among patients with stroke face specific challenges because they are typically elderly with cognitive and physical conditions that can affect medication-taking behavior. In a review of the primary reports of large stroke trials (>1000 participants) of oral drug therapy published since 1990 in the New England Journal of Medicine, Lancet, JAMA, and BMJ, we found that the rate of premature and permanent discontinuation ranged from 10% to 34% (mean 18%) and was higher for participants in the active treatment groups in most studies (Supplement Table 1)^{4–15}. Data from a few reports indicate that discontinuations are higher in the first year after randomization compared to later^{5,10,13}. Only four studies

provided a list of reasons for early drug discontinuation^{5–7,13}. No studies reported on resumption of drug after temporary interruption of drug therapy and none analyzed participant characteristics associated with adherence.

A better understanding of the epidemiology of adherence in clinical stroke research may be a starting point for strengthening research design and implementation. In this paper, therefore, we examine adherence to experimental medication and placebo in a clinical trial of secondary stroke prevention, which included a protocol for adherence monitoring and support. Our aims were to understand when drug adherence was most likely to fall off, how often participants resumed study drug after discontinuation, reasons for non-adherence, and patient characteristics associated with adherence.

METHODS

The IRIS Trial

The Insulin Resistance Intervention after Stroke (IRIS) trial has been previously described.⁶ Briefly, IRIS was a randomized, double-blind, placebo-controlled trial that tested pioglitazone for prevention of stroke and myocardial infarction among patients with a recent ischemic stroke or transient ischemic attack and insulin resistance. Major exclusion criteria included diabetes, age <40 years and a history of heart failure or bladder cancer. At baseline, a detailed medical history, vital signs, and physical measurements were obtained. Each participant provided written informed consent and institutional review boards approved the protocol at each site.

Eligible participants were randomized to an initial daily dose of 15mg of pioglitazone or matching placebo and titrated to a full protocol dose of 45 mg over two months. At 3 months, participants were switched to one 45-mg tablet of pioglitazone or matching placebo. Participants were contacted for follow-up assessments every 2 weeks during the first 3 months. Starting at month 4, participants were contacted every 4 months until 5 years or the last scheduled contact before the study ended in 2015.

Adherence Monitoring and Management in IRIS

Follow-up assessments were conducted by trained research coordinators using standardized interviews and protocols for managing common adverse events and lapses in study drug use. Pioglitazone had been associated with increased risk for weight gain, dependent edema, heart failure, and bone fracture and these events were tracked as potential adverse events at each contact. Adherence was monitored by asking participants about any problems taking the study drug at each contact and by counting pills remaining in returned pill bottles. Dates and reasons for each study drug cessation and restarting were recorded. The IRIS trial adherence goal was to have at least 80% of participants at each recruitment site taking at least 80% of the protocol dosage. If participants demonstrated adherence rates <80% based on self-report data (calculated as the number of days they reported being on the drug/number of days in the trial), coordinators were trained to implement the following protocol: 1) identify causes of poor adherence, including barriers to taking the pill regularly; and 2)

develop a plan to overcome the cause or barrier (e.g., dose adjustment, pill holiday with planned retreatal).

A detailed monthly report was sent to each research team with the adherence history for every participant at the site and the site's average performance compared to other sites. If a site had consistently low rates of adherence, the IRIS project manager and principal investigator scheduled a telephone conference with the site study team. Every participant at the site was then reviewed to identify those who were not achieving the adherence goal and their barriers to adherence. Gaps in information were identified and plans were developed to improve adherence for each participant. Follow-up telephone conferences were scheduled until adherence goals were reached or options for improvement had been exhausted.

Adherence Analytic Strategy

For the current study, we analyzed adherence using an internationally-recommended guideline from the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP). The ESPACOMP Adherence Reporting Guideline (EMERGE) separates the process of adherence into three phases (Figure 1): initiation (did patient start drug?), implementation (did patient take a drug holiday?), and persistence (did patient permanently and prematurely discontinue drug?)¹⁶. For this study, we defined a drug holiday as any period off drug lasting 14 days before restarting. Permanent and premature discontinuation was defined as being off drug for at least 14 consecutive days preceding the end of study (i.e., participant's death, withdrawal of consent, or study exit) or date of safety committee mandated permanent removal of study drug. For purposes of examining adherence we did not consider Safety Committee removal of study drug as non-adherence because this decision was not within the participant's control. In IRIS, participants were permanently removed from study drug after a confirmed episode of heart failure, second fragility fracture, macular edema diagnosis, bladder cancer diagnosis or if determined to be at high risk for bladder cancer (e.g., cytoxan exposure, pelvic radiation) or randomized in error. The adherence experience for participants removed from study drug was only examined for the period preceding their date of removal. We used self-reports of study drug use to classify adherence because this methodology permitted an analysis of the timing, frequency and reasons for interruptions. Risks of a first drug holiday and permanent discontinuation were estimated using Kaplan-Meier methods¹⁷

In addition, we examined mean adherence – defined as average dose reported taken as a proportion of the protocol-specified dose – by 4-month time periods in the study, by country, and by recruitment site. For patients who started the study drug, baseline features were examined for their association with staying on study drug (i.e., not permanently discontinuing drug prematurely). Twenty-one candidate features were selected based on available data and our pre-specified hypotheses. For this analysis, we calculated the odds ratio for staying on study drug in individual logistic regression models that included the examined feature and treatment assignment in the trial (pioglitazone or placebo). Stepwise regression models with p-values for selection and retention of 0.05, and forced inclusion of treatment assignment, were then used to identify baseline features independently associated with staying on study drug.

Role of Funding Source

The IRSI trial was funded by the National Institutes of Neurological Disorders and Stroke (NINDS). Drug and placebo tablets were provided by Takeda Pharmaceuticals, Inc. NINDS participated in revisions to the study design after funding. Neither NINDS nor Takeda participated in the collection, analysis, interpretation of the data. Neither participated in writing this paper or in the decision to publish.

RESULTS

A total of 3876 participants were enrolled in the IRIS trial. The mean age was 63 years and 65% of participants were male. Baseline features by treatment group are shown in Supplemental Table 2. Adherence to study drug according to EMERGE categories (Figure 1) is shown in Table 1. Only 1% of participants failed to initiate study drug and most took it without a drug holiday or permanent discontinuation over an average of 4.8 years of follow-up (52% in the pioglitazone group and 59% in the placebo group). Among participants who started study drug, 20% of the pioglitazone group and 17% of the placebo group took at least one drug holiday. Permanent discontinuation of the study drug was also more common in participants assigned to pioglitazone compared with placebo (36% versus 30%). When we examined the rates of permanent discontinuations by implementation status, we found that participants who had taken at least 1 drug holiday discontinued drug at higher rates compared to those without a holiday (pioglitazone group: 41% vs. 35%; placebo group: 39% vs. 28%).

Subjects were at highest risk for both drug holiday and permanent discontinuation during the first 12 months after randomization, especially among participants assigned to pioglitazone (Figure 2 and Figure 3). 10% of patients assigned to placebo and 13% assigned to pioglitazone took a drug holiday in first year compared with 2% in each group over each of the next four years. 10% of patients assigned to placebo and 17% assigned to pioglitazone discontinued treatment permanently in the first year compared with about 5% in each group over each of the next four years. When adherence was examined by 4-month time periods, the discordance between year one and other years was more apparent for patients assigned active treatment (Figure 4).

Reasons reported for drug holidays are shown in Table 2. Adverse events associated with pioglitazone (i.e., weight gain, edema, and shortness of breath) were the most common single reason reported by patients assigned to pioglitazone (40%) but were also common among patients assigned to placebo (24%). All other reasons for holiday were more equal among the two groups. In particular, large numbers of patients in each group took a holiday for adverse events not likely related to pioglitazone or for fear of having an adverse effect (26% in the pioglitazone group compared with 28% in the placebo group). A similar pattern of reasons was reported for permanent discontinuations (Table 2). For approximately 8% of drug holidays and 15% of discontinuations in both groups, patient's refused study drug without stating a reason. (Enumerations of the adverse events considered not likely related to study drug as reasons for holidays and discontinuations, and other reasons for holidays and discontinuations are shown in Supplemental Tables 3–5.)

When we examined reasons for drug holidays and permanent discontinuations by time period in trial, we found that the occurrence of an adverse event (related and unrelated to pioglitazone) was a more common reason in the first 12 months compared to after 12 months in both groups. In contrast, hospitalization or medical condition or being unable to locate were less common reasons in the first 12 months compared to after 12 months in both groups. Fear of adverse events was a more common reason for permanent discontinuation after 12 months of participation in both groups (Supplemental Table 6).

Mean levels of reported adherence (as a percentage of protocol dose) is shown, overall and by country of enrollment, in Table 3. As expected, subjects assigned to pioglitazone had lower levels of mean adherence than those assigned to placebo (68% vs. 77%). Across countries, adherence levels differed significantly for the placebo group, but not the pioglitazone group. Within countries, there was also variability in the levels of adherence achieved at individual sites. The experience of all 178 sites is displayed in Figure 5.

At the patient level, several baseline features were associated with a greater likelihood of staying on study drug in IRIS (i.e., not permanently discontinuing the study drug prematurely) when examined individually (Supplemental Table 7). When considered jointly, older age, male sex, non-black race, lower blood pressure, alcohol use, and assignment to placebo were predictive of adherence persistence, with the same direction of effect observed in both treatment groups.

DISCUSSION

In a trial of drug therapy for secondary stroke prevention, the risk for stopping the study drug (temporarily or permanently) was twice as high in the first year after randomization compared with each of the subsequent four years. This was true both for patients assigned to active therapy and placebo. When patients took a drug holiday or permanently stopped study drug in the IRIS trial, the most common reasons were not related to a known adverse effect of the active study drug. Rather, the reasons were more often related to adverse events unrelated to study drug, fear of adverse events, or medical and social conditions that made further participation challenging.

Our research is the first to report rates of drug initiation and holiday-taking among research participants in a trial of cerebrovascular disease. To our knowledge, we are also the first to report detailed information on drug holidays in any trial of cardiovascular research. Almost all randomized participants in the IRIS trial initiated study drug (99%). Later, however, 20% of patients assigned to pioglitazone and 17% assigned to placebo, on at least one occasion, stopped the study drug for at least 14 days and then resumed (i.e., took a drug holiday). Patients who took a drug holiday were at higher risk for permanent discontinuation compared with patients who did not take a holiday.

Research on adherence to oral drug therapy in clinical practice has identified individual interventions that are effective in improving adherence^{18–21}, but greater success is associated with multimodal interventions^{22–25}. Individual intervention types include feedback²⁰, simplification of the drug regimen (e.g., one daily dose instead of multiple daily doses),^{26,27}

co-management with a pharmacist¹⁸, patient education and cognitive behavioral therapy²⁰, and medication-taking reminders/cues²⁵. The most effective strategies incorporate improved communication with healthcare providers, whether it is a nurse, physician, or pharmacist¹⁹.

There is less research on adherence in clinical trials specifically. However, it is known that adherence is a problem^{1,3,28,29} and several of our findings are consistent with previous efforts to understand the epidemiology of this problem. Our findings that risk for discontinuation is greatest early after randomization, for example, has been demonstrated for trials of antihypertension therapy³ and three other trials of stroke prevention^{5,10,13}.

Strategies thought to improve adherence in clinical trials include many of the strategies identified to improve adherence in clinical practice, including feedback and behaviorally-oriented counseling^{23,29,30}. However, clinical trial adherence can also be improved by run-in procedures to select patients for treatment tolerance and adherence, and other screening procedures to select subjects for better adherence behavior.

We observed substantial variability in mean study drug adherence among randomizing centers. Among sites with at least 20 participants, the range of mean pill consumption as a proportion of protocol-specified dose was varied between 60% and 90%. Although we do not have objective data, we believe the variability relates to site team behavior. More effective research teams aspired to higher overall rates of adherence, communicated more frequently with participants, educated their participants about clinical trial research, and used sophisticated participant-centered practices to support adherence. These practices included adherence monitoring, goal setting, feedback, identification of barriers to adherence, involvement of caregivers and loved-ones, and implementation of creative solutions. The variability among sites suggest that adherence can be safeguarded by the actions of local research teams.

A special concern for adherence in clinical trial research is risk of bias if adherence intervention strategies are implemented differentially between treatment groups²⁸. That is, differential implementation may widen or narrow the observed treatment outcome difference for an effective therapy. To safeguard against such bias, investigators can maintain blinding to treatment assignment, monitor adherence uniformly, and mitigate adherence according to a closely-followed protocol.

Our study has important strengths and some weakness. Strengths of our study include the long follow-up in the IRIS Trial (median 4.8 years), compared with other studies which have stopped follow-up at one year or less.^{3,20} Other strengths include a low rate of participant loss-to-contact and an adherence protocol that allows readers to understand the conditions affecting our results. Weaknesses include incomplete information on reasons for interrupting therapy. Although our protocol required us to ask participants about reasons, the responses could be non-specific. A total of 20% (256/1275) of participants who permanently discontinued study did not give a reason or stated it was based on “physician advice.” Other stroke trials have encountered similar challenges in ascertaining specific reasons for discontinuation⁵⁻⁷, but we believe that gentle inquiry might have resolved many of these non-specific responses.

Adherence is too important to leave to chance in stroke clinical trial research. Our results show the time frame during research when participants are most at risk for drug discontinuation, the common reasons, and factors associated with success and failure. Our finding of variability among sites and countries provides indirect evidence that research teams can be selected for or trained to achieve optimal results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Three phase of adherence according to the ESPACOMP Medication Adherence Reporting Guideline (EMERGE)¹⁶.

Figure 2:
Cumulative risk of first drug holiday according to treatment assignment in the IRIS trial.

Figure 3:
Cumulative risk of premature, permanent discontinuation of study drug according to treatment assignment in the IRIS Trial.

Figure 4:

Mean adherence according to time from randomization and treatment group. Mean adherence was measured as average dose reported taken as a proportion of the protocol-specified dose.

Figure 5:
Distribution of mean adherence at research sites participating in the IRIS Trial. Blue bars represent all sites. Green bars represent sites with 20 or more participants.

Table 1.

Study Drug Adherence in IRIS by EMERGE Phase

<i>EMERGE Phase</i>	(Description)	Pioglitazone (n=1939)		Placebo (n=1937)	
		No.	%	No.	%
<i>Initiation</i>	Did not start drug	13	1%	14	1%
	Started drug	1926	99%	1923	99%
<i>Implementation</i>	Took Drug Holidays *	381	20%	325	17%
	No Drug Holidays *	1545	80%	1598	83%
<i>Persistence</i>	Discontinued drug †	695	36%	580	30%
	Continued drug	1231	64%	1343	70%

* Drug holiday is defined as being off drug for at least 14 consecutive days before restarting.

† Discontinued drug is defined as being off study drug for at least 14 days preceding end of study (defined as death, withdrawal of consent, or exit date, whichever came first) or before date of protocol mandated removal of study drug.

Table 2.**Reasons for Drug Holidays and Discontinuations**

Reason	Drug Holidays		Permanent Discontinuations	
	Pioglitazone	Placebo	Pioglitazone	Placebo
	n=461	n=388	n=695	n=580
Adverse event possibly related to pioglitazone [*]	40%	24%	30%	12%
Adverse event not likely related to pioglitazone [†]	23%	24%	18%	15%
Refusal with no reason provided	8%	8%	13%	19%
Hospitalization or medical condition	11%	16%	9%	12%
Physician advice	2%	6%	4%	5%
Other [‡]	4%	9%	5%	6%
Following study protocol [§]	6%	4%	3%	4%
Unable to locate	3%	6%	11%	14%
Fear of adverse effects	3%	4%	8%	13%

^{*} Weight gain, edema, shortness of breath.

[†] See Supplemental Tables 3 and 4 for reasons for drug holidays and discontinuations, respectively.

[‡] See Supplemental Tables 5 for other reasons for drug holidays and discontinuations.

[§] Heart failure suspected, ALT or CK abnormality, unexplained hematuria, TZD prescribed, hypoglycemia, patient moved, patient enrolled in conflicting trial.

Table 3.Mean Adherence^{*} by Country, Overall and by Treatment Group

Country	Total		Pioglitazone		Placebo	
	Mean		Mean		Mean	
	No.	Adherence	No.	Adherence	No.	Adherence
	Pts.	(SD)	Pts.	(SD)	Pts.	(SD)
United States	2591	72(36)	1305	68(37)	1286	76(33)
United Kingdom	256	76(36)	123	72(37)	133	81(34)
Canada	543	76(36)	272	71(38)	271	82(31)
Australia	108	75(35)	53	66(37)	55	83(31)
Germany	150	73(37)	73	71(39)	77	75 (36)
Italy	47	65 (40)	22	66 (41)	25	63(40)
Israel	178	68 (36)	90	63(37)	88	74 (34)
Total ^{**}	3873	73 (36)	1938	68 (37)	1935	77(33)
ANOVA P		0.02		0.54		0.01

* Mean adherence defined as the average dose the participant reported taking as a proportion of the protocol-specified dose.

** 1 participant randomized to pioglitazone group and 2 participants randomized to placebo group dropped out on day of randomization.